Cancer Causes and Control 12: 103–110, 2001.

Effects of mammographic density and benign breast disease on breast cancer risk (United States)

Celia Byrne[1,*], Catherine Schairer[2], Louise A. Brinton[2], John Wolfe[3], Navin Parekh[3], Martine Salane[3], Christine Carter[4] & Robert Hoover[2]
[1]*Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA; Ph.: 617-525-0862;* [2]*Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD 20892, USA;* [3]*Wolfe Radiologic Associates, Detroit, MI, USA;* [4]*OncorMed, Gaithersburg, MD, USA (*Author for correspondence)*

Received 16 March 2000; accepted in revised form 14 September 2000

Key words: benign breast disease, breast cancer risk, mammographic density.

Abstract

Background: Having either a history of benign breast disease, particularly atypical hyperplasia or extensive mammographic breast density, is associated with increased breast cancer risk. Previous studies have described an association between benign breast disease histology and breast density. However, whether these features measure the same risk, or are independent risk factors, has not been addressed.
Methods: This case–control study, nested within the prospective follow-up of the Breast Cancer Detection Demonstration Project, evaluated both benign histologic and mammographic density information from 347 women who later developed breast cancer and 410 age- and race-matched controls without breast cancer. Multivariate logistic regression analyses provided maximum-likelihood estimates of the odds ratios (OR) and 95% confidence intervals (CI) to evaluate the relative risk of breast cancer associated with each exposure.
Results: Adjusting for mammographic density, the OR for atypical hyperplasia was 2.1 (95% CI: 1.3–3.6), and adjusting for benign breast histology, the OR for ≥75% density was 3.8 (95% CI: 2.0–7.2). Women with nonproliferative benign breast disease and ≥75% density had an OR of 5.8 (95% CI: 1.8–18.6), and women with <50% density and atypical hyperplasia had an OR of 4.1 (95% CI: 2.1–8.0).
Conclusions: In this study, both benign breast disease histology and the percentage of the breast area with mammographic density were associated with breast cancer risk. However, women with both proliferative benign breast disease and ≥75% density were not at as high a risk of breast cancer due to the combination of effects (p = 0.002) as women with only one of these factors.

Introduction

In the United States, the number of women who will develop breast cancer each year continues to increase [1]. In light of the number of women affected with breast cancer, it becomes increasingly important to understand the disease and to identify women who might benefit most from screening. Two separate factors have been associated with increased risk of developing breast cancer: (1) having had a benign biopsy with evidence of atypical hyperplasia, which is associated with a three- to five-fold increased risk; and (2) having a high proportion of breast tissue that appears dense on a mammogram, which is associated with a four- to five-fold increased risk of developing breast cancer [2–6].

The mammographic appearance of breast tissue is clearly related to features of breast histology. However, the description of histologic features related to mammographic density has varied in large part due to a lack of uniform criteria [7, 8]. Mammographic density has been associated with "adenosis" characterized by intraductal hyperplasia [9], high-grade epithelial abnormalities [10], extralobular fibrosis and epithelial hyperplasia [11], ductal epithelial hyperplasia and lobular microcalcifications [12], and increased collagen/fibrosis and epithelium [13]. Most of these studies indicated an association of mammographic density with epithelial proliferation [10–12], although a few others indicated a close link with stromal proliferation [13]. An analysis of women from the Canadian National Breast Screening Study (NBSS) showed an association between having extensive mammographic densities with hyperplasia and atypical hyperplasia/carcinoma *in situ* [14]. The authors of the NBSS study proposed that the breast cancer risk associated with extensive mammographic density may in part be attributable to the processes that result in proliferative histologic features [14].

Whether the breast cancer risk associated with proliferative benign breast disease and with mammographic density reflects a common histologic process is an important issue that has not been adequately addressed. If these two different measures of breast tissue morphology are both associated with breast cancer risk, knowledge of their separate and combined effects may help to identify women at particularly high risk of subsequent breast cancer.

In this case–control study, nested within the prospective follow-up study of participants in the Breast Cancer Detection Demonstration Project (BCDDP), both benign histologic data and measured mammographic density were assessed from information obtained before diagnosis from 347 women who later developed breast cancer and 410 age- and race-matched controls without breast cancer. This study evaluated whether high-risk histologic subtypes of benign breast disease accounted for the risk associated with mammographic density. In addition, this study assessed the combined breast cancer risk of increased mammographic density with histologic subtypes of benign breast disease.

Methods

The BCDDP was a nationwide breast cancer screening program, cosponsored by the American Cancer Society and the National Cancer Institute, that was conducted between 1973 and 1980. Over 280,000 women enrolled at one of 29 centers throughout the United States for five years of annual breast cancer screening. In 1980, 64,182 BCDDP participants were selected for long-term follow-up, including the 25,114 women who had a surgical breast biopsy diagnosed as benign during the screening phase. These women were followed through 1989. In the first phase of follow-up, conducted between 1980 and 1986, 96% of the eligible women provided information concerning any breast surgical procedures and changes in breast cancer risk factors through annual telephone interviews. Between 1987 and 1989, 85% of the women who had at least one telephone interview completed a mailed questionnaire, which elicited information about breast cancer outcomes and changes in breast cancer risk factors since the last interview. Extensive tracing efforts included a National Death Index search of all nonrespondents. In addition, pathology reports were sought for all breast procedures.

The effect of mammographic features on breast cancer risk among BCDDP participants was previously evaluated in a nested case–control study using subjects from 1974 through 1989 in both the screening and the follow-up phases [6]. All incident breast cancer cases diagnosed at least one year after entering the BCDDP screening program were eligible cases. Controls matched to cases by study center, age (year of birth), and race were selected from among women at risk for developing breast cancer at the time of the cases' diagnoses. Mammographic features of the ipsilateral breast were assessed from the initial prediagnostic screening mammogram for 1880 incident breast cancer cases (73% of eligible cases) and the corresponding mammogram for 2152 (84% of eligible controls) comparison subjects who had attended 22 of the 29 original BCDDP centers that sent the participants' mammographic images to a central data repository [6]. From the previous case–control study [6], the percentage of the breast area with dense mammographic appearance was assessed by one of three trained reviewers who marked the area with dense mammographic appearance on the caudal mammogram obtained at the initial BCDDP screening visit. With a computerized planimeter, the total breast area and the marked area of density were measured, and the percentage of the total breast area with mammographic density was calculated [6]. The percentage breast density was categorized as: $<10\%$, 10–49%, 50–74%, and $\geq 75\%$. The assessment of percentage mammographic density in the previous case–control study also included a nested validation study. Both intra- and inter-observer correlation coefficients comparing repeated evaluations of the continuous measure of percentage density were approximately 0.9, which indicates the high reliability of this measure [6].

From the participants in the previous study of mammographic features, for whom the percentage of the area of the breast with dense mammographic appearance was measured, 981 incident cases and 1113 controls were identified through 1989 during the BCDDP follow-up phase. Of these cases and controls identified during the follow-up phase of the BCDDP, 532 cases and 600 controls had a previous surgical breast biopsy at some time during the BCDDP screening phase (between 1973 and 1980) that was diagnosed as benign. Even though a benign biopsy provides histologic information only from a sample of breast tissue, proliferative benign breast disease has generally been associated with an equivalent risk of breast cancer to either breast, thus suggesting that the biopsy reflects the overall histology of the breast tissue as a generalized marker of risk. The histologic classifications of breast tissue considered in this study were previously categorized and evaluated by Carter *et al.* (1988) in their prospective study of benign breast disease and breast cancer risk in the BCDDP [15]. At the time of each biopsy a detailed standardized pathology report form was completed at the BCDDP screening center. Information from these standardized pathology report forms was combined into four categories: (1) atypical hyperplasia, comprising either lobular epithelial hyperplasia with atypia or ductal hyperplasia with atypia; (2) proliferative disease without atypia, which included lobular epithelial hyperplasia (not otherwise specified), sclerosing adenosis, or ductal papillary hyperplasia; (3) nonproliferative disease, which included ductal ectasia, papillary apocrine metaplasia or epithelial cyst – with or without apocrine metaplasia; and (4) other benign breast diseases, including congenital or developmental anomaly, acute or chronic inflammation or abscess, granulomatous inflammation, fat necrosis, galactocele, or fibroadenoma. If a woman had more than one biopsy, the first was considered. If multiple types of benign breast disease were indicated, the exposure was classified with priority assigned according to the order presented above.

Both percentage mammographic density and detailed histologic information from the biopsy conducted during the BCDDP screening phase were available for 347 (65.2%) cases and 410 (68.3%) controls in this nested case–control study. These surgical biopsies were performed during the BCDDP screening phase, but not necessarily concurrent with the mammograms evaluated for this study. Generalized linear models provided estimates of adjusted mean percentage density across categories of benign histology among controls.

Unconditional logistic regression models that included a continuous measure of age (years) and a categorical variable for race (white, black, or Asian) provided maximum-likelihood estimates of the odds ratio (OR) and 95% confidence intervals (CI). Further analyses adjusted for the potential categorical confounding effects of a first-degree family history of breast cancer (none, one, two or more), drinking alcohol (never, less than one drink/day, one or more drinks/day), nulliparity and age at first birth (nulliparous; parous with age at first birth at: <20 years; 20–24 years; 25–29 years; ≥30 years), years of education (less than high school, high school, some college, college degree, graduate degree), weight at entry to the screening program (quartiles), menopause status and age at menopause (premenopausal; postmenopausal [natural or bilateral oophorectomy] with age at menopause: <45 years, 45–49 years, 50–54 years, 55+ years; and other surgical menopause with unknown age), and use of postmenopausal hormones (never used; used postmenopausal hormones for: ≤5 years; >5 years; unknown use or duration). The joint effects of exposures were evaluated by creation of a cross-classified variable with a common reference group. A statistical test of interaction on a multiplicative scale was performed by treatment of the exposure variable scores as continuous and evaluation of the significance of the interaction term in the model.

Results

Both cases and controls in this study had a mean age of 59.5 years (Table 1). Cases weighed slightly more than controls, had more years of education, slightly later age at menopause, more often premenopausal, more often consumed one or more alcoholic drinks per day, were more likely to have a first-degree family history, and had a slightly later mean age at first birth (Table 1).

Among the non-breast cancer cases (controls) in this study, 23% had nonproliferative disease, 54% had proliferative disease without atypia, 10% had atypical hyperplasia, and 13% had other types of benign disease (Table 2). In this study, 16% of the controls had <10% mammographic density, 44% had 10–49% mammographic density, 31% had 50–74% mammographic

Table 1. Distribution of covariates among cases and controls

Covariates	Cases (n = 347)	Controls (n = 410)
Age years[a] (SD)	59.5 (9.7)	59.5 (9.5)
Weight[a] lb (SD)	141.8 (24.9)	140.3 (23.8)
BMI[a] kg/m^2 (SD)	24.0 (4.1)	23.9 (3.8)
Years of education[a] (SD)	13.4 (2.3)	12.8 (2.4)
Age at menopause[a,b]	48.9 (4.7)	47.9 (6.0)
Premenopausal[c]	15.0%	13.9%
Natural menopause[c]	41.8%	43.9%
Surgical menopause[c]	41.6%	40.5%
Alcohol beverages/day (1+)[c]	17.6%	11.2%
Any first-degree family history[c]	30.5%	21.5%
Nulliparous[c]	3.2%	3.7%
Age at first birth[d]	24.1 (4.7)	23.5 (4.2)

[a] Mean and standard deviation.
[b] Mean and standard deviation of age at menopause among postmenopausal women who had a natural menopause or a bilateral oophorectomy.
[c] Percentage of cases or controls.
[d] Mean and standard deviation of age at first birth among parous women.

Table 2. Joint distribution of breast histology and percentage breast density among controls

Benign histology	No.(%) of subjects by percentage breast density				Total
	< 10%	10–49%	50–74%	≥75%	
Nonproliferative disease	15 (16)[a]	49 (52)	25 (27)	5 (5)	94 [23][b]
Proliferative disease without atypia	29 (13)	92 (41)	79 (35)	23 (10)	223 [54]
Atypical hyperplasia	4 (9)	17 (42)	13 (32)	7 (17)	41 [10]
Other	19 (37)	24 (46)	9 (17)	–	52 [13]
Total	67 (16)	182 (44)	126 (31)	35 (9)	410

[a] Row percentages, in parentheses.
[b] Column percentages, in square brackets.

density, and 9% had ≥75% mammographic density. The proportion of controls with ≥50% breast density increased with the degree of proliferation, with 31.9% of those with nonproliferative conditions, 45.7% of those with proliferative disease without atypia, and 48.8% of those with atypical hyperplasia having ≥50% mammographic density. The mean percentage breast density among controls increased with the degree of proliferation from 36.1% for those with nonproliferative conditions, 42.7% for proliferative disease without atypia, to 48.2% with atypical hyperplasia. Women whose breast tissue was classified as "other" had a mean percentage breast density of 24.9%. The proportion of controls with atypical hyperplasia increased from 6% to 20% as the percentage density rose from < 10% to ≥75%. Women with "other" types of benign conditions had significantly lower percentage breast density ($p \le 0.002$), but the age and race adjusted percentage density means across the other benign histologic types were not statistically significantly different ($p \ge 0.157$).

The analyses of benign histology and breast cancer risk are presented in Table 3. In analyses controlling only for age and race, compared with those with nonproliferative disease, subjects with proliferative disease without atypia had an OR of 1.3 (95% CI: 0.9–1.9) and those with atypical hyperplasia had an OR of 2.2 (95% CI: 1.3–3.6). While the histologic classification was associated with the percentage mammographic density, additional adjustment for the percentage breast density had little effect on the ORs for proliferative lesions without atypia and for atypical hyperplasia (Table 3). Further adjustment for the breast cancer risk factors of family history, drinking alcohol, nulliparity and age at first birth, years of education, weight, menopause status, age at menopause, and use of postmenopausal hormones only slightly modified the magnitude of the associations with benign histology.

Breast cancer risk also increased with the percentage of breast area with mammographic density among these women with benign breast disease. Compared with women for whom less than 10% of the breast area appears dense on the mammogram, the ORs were 2.0 (95% CI: 1.2–3.4), 2.8 (95% CI: 1.6–4.7), and 4.1 (95% CI: 2.1–7.8) for those with 10–49%, 50–74%, and ≥75% of the breast area that appeared mammographically dense, respectively (Table 4). Additional adjustment for the type of benign histology slightly reduced the effects associated with increased mammographic density. Further adjustment for family history, drinking alcohol, nulliparity, age at first birth, years of education, and weight slightly increased the magnitude of the associations with increased mammographic density such that women with ≥75% mammographic density had an OR of 4.4 (95% CI: 2.1–9.0).

To determine whether mammographic density was a breast cancer risk factor across each histologic category of benign breast disease, and whether the category of benign breast disease was associated with risk across each level of breast density, a cross-classified variable was created with women who had nonproliferative lesions and < 50% breast density as the reference group (Table 5). Among women with nonproliferative benign breast disease, risk increased almost six-fold (95% CI: 1.8–18.6) for those with ≥75% mammographic density. Breast cancer risk also increased with increasing percentage mammographic density, among women with proliferative benign breast disease without atypia, with an OR of 1.6 (95% CI: 1.0–2.5) for < 50% breast density, 2.8 (95% CI: 1.5–4.1) for 50–74% breast density, and 3.2 (95% CI: 1.6–6.6) for ≥75% breast density. However, among women with atypical hyperplasia, there was no evidence of increased risk with greater percentage density.

For women with < 50% breast density, risk associated with the benign histology increased with the presence and severity of epithelial proliferation. Among women with < 50% breast density, those with proliferation without atypia had an OR of 1.6 (95% CI: 1.0–2.5), and those with atypical hyperplasia had an OR of 4.1 (95% CI: 2.1–8.0), compared with women with nonproliferative histology. In contrast, for women with ≥75% breast density, risk decreased with the presence and severity of proliferation. Among those women with ≥75% breast density, the OR was 5.8 (95% CI: 1.8–18.6) from the 11 cases and five controls with nonproliferative histology, 3.2 (95% CI: 1.6–6.6) from the 29 cases and 23 controls with proliferation without atypia, and 2.1 (95% CI: 0.6–7.0) from the six cases and seven controls with atypical hyperplasia, compared with those with nonproliferative histology and < 50% breast

Table 3. Breast cancer risk by benign breast disease histology

Benign histology	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)	OR[c] (95% CI)
Nonproliferative disease	62	94	1.0	1.0	1.0
Proliferative disease without atypia	198	223	1.3 (0.9–1.9)	1.3 (0.9–1.9)	1.2 (0.8–1.8)
Atypical hyperplasia	58	41	2.2 (1.3–3.6)	2.1 (1.3–3.6)	2.1 (1.2–3.6)
Other	29	52	0.8 (0.5–1.4)	0.9 (0.5–1.7)	0.8 (0.4–1.5)

[a] Logistic regression model includes age and race.
[b] Logistic regression model includes percentage breast density, age, and race.
[c] Logistic regression model includes percentage breast density, age, race, family history, drinking alcohol, nulliparity and age at first birth, years of education, weight, menopause status, age at menopause, and use of postmenopausal hormones. (Due to missing covariates, five cases and five controls were excluded from the full model analyses.)

Table 4. Breast cancer risk by percentage breast density

Percentage breast density	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)	OR[c] (95% CI)
< 10	26	67	1.0	1.0	1.0
10–49	143	182	2.0 (1.2–3.4)	1.9 (1.1–3.2)	2.0 (1.2–3.5)
50–74	127	126	2.8 (1.6–4.7)	2.6 (1.5–4.5)	3.0 (1.7–5.4)
≥75	51	35	4.1 (2.1–7.8)	3.8 (2.0–7.2)	4.4 (2.1–9.0)

[a] Logistic regression model includes age and race.
[b] Logistic regression model includes benign histology, age, and race.
[c] Logistic regression model includes benign histology, age, race, family history, drinking alcohol, nulliparity and age at first birth, years of education, weight, menopause status, age at menopause, and use of postmenopausal hormones. (Due to missing covariates, five cases and five controls were excluded from the full model analyses.)

Table 5. Breast cancer risk by benign breast disease histology and percentage breast density

Benign histology category	Percentage breast density		
	< 50	50–74	≥75
Nonproliferative	1.0[a] (–); 26/63[c]	2.5 (1.3–5.1)[b]; 24/23	5.8 (1.8–18.6); 11/5
Proliferative without atypia	1.6 (1.0–2.5); 88/119	2.5 (1.5–4.1); 78/79	3.2 (1.6–6.6); 29/23
Atypical hyperplasia	4.1 (2.1–8.0); 36/21	3.0 (1.3–7.0); 16/13	2.1 (0.6–7.0); 6/7

[a] Reference category. All results adjusted for age, race, family history, drinking alcohol, nulliparity and age at first birth, years of education, weight, menopause status, age at menopause, and use of postmenopausal hormones.
[b] 95% confidence interval.
[c] Number of cases/number of controls in each category.

density. The test of the multiplicative interaction term between the three categories of benign breast disease and the three levels of percentage breast density was significant at $p = 0.002$.

Discussion

While other studies have evaluated the association between benign breast histology and mammographic features [9–13], this is one of the first studies to evaluate the separate and joint effects of these factors on breast cancer risk. In this study, benign breast disease histology and measured percentage of the breast area with mammographic density appeared to be distinct breast cancer risk factors. The risk associated with benign breast disease histology was not explained by the effects of percentage breast density (Table 3), and the risk associated with increased percentage breast density was not explained by the benign breast disease histology (Table 4). Furthermore, the breast cancer risks associated with histologic types of benign breast disease and percentage breast density were not explained by effects of nulliparity and age at first birth, first-degree family history of breast cancer, years of education, alcohol use, body weight, menopause status, age at menopause, and use of postmenopausal hormones (Tables 3 and 4). Having a high percentage breast density (≥75%) was associated with almost a six-fold greater breast cancer risk among women with nonproliferative benign breast disease, and atypical hyperplasia was associated with a greater than four-fold rise in risk among women with < 50% breast density (Table 5). However, the effects of percentage breast density seemed to modify the effects associated with atypical hyperplasia, and the effects associated with proliferative benign breast disease and atypical hyperplasia seemed to modify the effects associated with having ≥75% breast density (Table 5).

On a mammogram, epithelial and stromal tissue appears dense compared to the translucent appearance of fat. Thus, a mammogram provides an image of the entire breast from which the percentage of the breast with mammographic density reflects the relative degree of epithelial and stromal tissue compared with fat in the breast. Several theories have been proposed to explain the association between greater percentage breast density and increased breast cancer risk. Trichopoulos and Lippman [16] have suggested that the association supports the hypothesis of the importance of the number of epithelial cells in the etiology of breast cancer. In contrast, others have proposed that the increase in stromal proliferation is likely to explain the association between percentage breast density and breast cancer risk [7]. The results of this study cannot definitively differentiate between these hypotheses. However, since the risk associated with the mammographic measure of percentage density was not explained by the risk associated with the histologic measure of epithelial proliferation, the results of this study support the theory that mammographic density may reflect an increased proliferation of stromal tissue.

Other studies have reported a similar increase in risk with increased mammographic density [17–20]. This study was a subset of a larger case–control study nested within the screening and follow-up phases of the Breast Cancer Detection Demonstration Project (BCDDP) in which the initial screening mammogram was assessed for 1880 cases and 2152 controls [6]. All cancers diagnosed within one year of the initial mammogram were excluded from this larger study, to eliminate the potential bias in assessing the mammographic features from the ipsilateral breast. The relative risks for breast cancer associated with increased mammographic density in the subset analyses presented in this paper were of similar magnitude to those from the larger case–control study, which indicates that this subset was not a biased sample with regard to the mammographic effects. The techniques for assessing the percentage of the breast with dense mammographic appearance have varied across studies [21]. Some studies used a visual estimate to categorize the percentage of the breast with mammographically dense appearance [17, 22], while others measured the area of the breast and the area of density to calculate the percentage of the breast with mammographic density with a manual planimeter [18, 19], a computerized planimeter [6], or a digitized computer image [5, 20]. While still requiring an element of subjective evaluation, the computerized planimeter measurement of the marked areas used for this substudy provided a continuous measure of percentage breast density and was shown in the larger study to have a high intra- and inter-observer correlation coefficient. Since the observers were blinded to the subsequent case–control status of the subjects, any misclassification of the measure would likely have biased effects towards the null.

Proliferative epithelial lesions, particularly atypical hyperplasia, have been associated with increased breast cancer risk in a number of studies [15, 23, 24]. From a study of over 3000 biopsies with up to 24 years of follow-up, Dupont and Page reported that women with proliferative disease without atypia had a relative risk (RR) of 1.9 (95% CI: 1.2–2.9), and those with atypical hyperplasia had a RR of 5.3 (95% CI: 3.1–8.8) compared with those who had nonproliferative disease [25]. Similarly, Carter *et al.* reported that women with proliferative disease without atypia were at moderately increased risk (RR = 1.9, 95% CI: 1.5–2.4), and women with atypical hyperplasia were at the highest breast cancer risk (RR = 3.0, 95% CI: 2.1–4.1) [15]. This large prospective study of 16,692 women who had a surgical breast biopsy diagnosed as benign during the BCDDP screening phase, conducted by Carter *et al.*, was the source population for the nested case–control study presented in this paper [15].

While the cases and controls for the study presented in this paper were sampled from the women in the prospective analyses, the magnitude of the effects associated with proliferative lesions and with atypical hyperplasia in this case–control study were slightly lower than that reported by Carter *et al.* [15] for this population (OR = 2.2 [95% CI: 1.3–3.6] in this study *vs.* RR = 3.0, [95% CI: 2.1–4.1] in the previous study). There are several plausible reasons for these slight differences. Due to the small numbers of subjects in the case–control study, sampling variation may explain the differences, especially since our 95% confidence intervals include the original effects. Alternatively, it is possible that the association with benign breast histology differed among women for whom mammographic information was available. This latter reason seems unlikely since analyses conducted among the eligible cases and controls for whom mammographic data were not available revealed relative risks of 2.2 (95% CI: 1.1–4.1) for proliferative lesions without atypia and 2.2 (95% CI: 0.9–5.5) for atypical hyperplasia. The third and most likely explanation for the slight differences in magnitude of effects is the difference in time between the biopsy and breast cancer in the two analyses. The large prospective analysis evaluated the cancers diagnosed starting six months after the biopsy (diagnosed between August 1973 and February 1986). In the present nested case–control substudy, only breast cancer cases diagnosed after the last BCDDP screening visit (in 1980) were included. Thus, as the cohort aged, these analyses included a higher proportion of postmenopausal breast cancer cases and fewer premenopausal cases among whom atypical hyperplasia has a stronger impact. If the association between proliferative lesions and breast cancer risk decreases with time, as suggested by Dupont and Page [26], then excluding the cases diagnosed during the earlier screening phase would likely explain the lower relative risks in the case–control analysis.

From this study, the joint effects of benign breast disease histology and increased breast density were less than expected ($p = 0.002$), given the separate effects of benign breast disease histology among women with < 50% breast density and the effects of increased percentage breast density for those with nonproliferative benign breast disease. While this effect modification may be a spurious finding due to the small numbers evaluated in this study, even the upper level of the wide confidence levels (0.7–8.9) for those with both factors indicates risk no greater than additive for the combined effects of high breast density and atypical hyperplasia. A better understanding of the joint effects of benign breast disease histology and percentage mammographic density will be an important step towards identifying which women with proliferative benign breast disease are at particularly high risk.

Acknowledgements

The authors thank Stuart Schnitt, MD and Mark Sherman, MD for their helpful comments on earlier drafts of this paper.

References

1. American Cancer Society (1995) *Cancer Facts and Figures – 1995*. Atlanta, GA.
2. Bodian CA (1993) Benign breast diseases, carcinoma *in situ*, and breast cancer risk. *Epidemiol Rev* **15**: 177–187.
3. Saftlas AF, Szklo M (1987) Mammographic parenchymal patterns and breast cancer risk. *Epidemiol Rev* **9**: 146–174.
4. Warner E, Lockwood G, Tritchler D, Boyd NF (1992) The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effects of method of classification. *Cancer Detect Prev* **16**: 67–72.
5. Boyd NF, Byng JW, Jong RA, *et al.* (1995) Quantitative classifications of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* **87**: 670–675.
6. Byrne C, Schairer C, Wolfe J, *et al.* (1995) Mammographic features and breast cancer risk: effects with time, age and menopause status. *J Natl Cancer Inst* **87**: 1622–1629.
7. Oza AM, Boyd NF (1993) Mammographic parenchymal patterns: a marker of breast cancer risk. *Epidemiol Rev* **15**: 196–208.
8. Cook MG, Rohan TE (1985) The pathoepidemiology of benign proliferative epithelial disorders of the female breast. *J Pathol* **146**: 1–15.
9. Ingleby H, Gershon-Cohen J (1960) *Comparative Anatomy, Pathology, and Roentgenology of the Breast*. Philadelphia, PA: University of Philadelphia Press.
10. Wellings SR, Wolfe JN (1978) Correlative studies of the histological and radiographic appearance of the breast parenchyma. *Radiology* **129**: 299–306.
11. Bright RA, Morrison AS, Brisson J, *et al.* (1988) Relationship between mammographic and histologic features of breast tissue in women with benign biopsies. *Cancer* **61**: 266–271.
12. Bartow SA, Pathak DR, Mettler FA (1990) Radiographic microcalcifications and parenchymal patterns as indicators of histologic "high-risk" benign breast disease. *Cancer* **66**: 1721–1725.
13. Boyd NF, Jensen HM, Cooke G, Han HL (1992) Relationship between mammographic and histologic risk factors for breast cancer. *J Natl Cancer Inst* **84**: 1170–1179.
14. Boyd NF, Jensen HM, Cooke G, Han HL, Lockwood GA in collaboration with the Reference Pathologists of the Canadian National Breast Screening Study and Miller AB (2000). Mammographic densities and the prevalence and incidence of histological types of benign breast disease. *Eur J Cancer Prev* **9**: 15–24.
15. Carter CL, Corle DK, Micozzi MS, Schatzkin A, Taylor PR (1988) A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* **128**: 467–477.
16. Trichopoulos D, Lippman RD (1992) Mammary gland mass and breast cancer risk. *Epidemiology* **3**: 523–526.
17. Brisson J, Merletti F, Sadowsky NL, Twaddle JA, Morrison AS, Cole P (1982) Mammographic features of the breast and breast cancer risk. *Am J Epidemiol* **115**: 428–437.
18. Wolfe JN, Saftlas AF, Salane M (1987) Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case–control study. *Am J Radiol* **148**: 1087–1092.
19. Saftlas AF, Hoover RN, Brinton LA, *et al.* (1991) Mammographic densities and risk of breast cancer. *Cancer* **67**: 2833–2838.
20. Boyd NF, Byng JW, Jong RA, *et al.* (1995) Quantitative classifications of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* **87**: 670–675.
21. Lee-Han H, Cooke G, Boyd NF (1995) Quantitative evaluation of mammographic densities: a comparison of methods of assessment. *Eur J Cancer Prev* **4**: 285–292.
22. Boyd NF, O'Sullivan B, Campbell JE, *et al.* (1982) Mammographic signs as risk factors for breast cancer. *Br J Cancer* **45**: 185–193.

23. Page DL, Dupont WD, Rogers LW, Rados MS (1985) Atypical hyperplastic lesions of the female breast. *Cancer* **55**: 2698–2708.
24. London SJ, Connolly JL, Schnitt SJ, Colditz GA (1992) A prospective study of benign breast disease and the risk of breast cancer. *JAMA* **267**: 941–944.
25. Dupont WD, Page DL (1985) Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* **312**: 146–151.
26. Dupont WD, Page DL (1989) Relative risk of breast cancer varies with time since diagnosis of atypical hyperplasia. *Hum Pathol* **20**: 723–725.